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Original Article

Relation of neural tube defects with folic acid use during pregnancy

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Abstract

Aim: The objective of this study was to investigate the rate of neural tube defects (NTD) and the clinical features of newborns of mothers who did not use folic acid (FA) in their pregnancies.

Material and methods: The data of a total of 82 newborns, who were diagnosed with meningomyelocele were operated and examined, retrospectively. The newborns were divided into two groups depending on whether their mothers used FA during pregnancy or not.

Results: The mothers of 37 (45.1%) newborns used FA during the antenatal period, whereas those of 45 (54.9%) newborns did not. The mean birth weight of the newborns whose mothers did not use FA were lower. Furthermore 9 (25%) newborns whose mothers did not use FA were delivered via cesarean section.The incidence of meningomyelocele was 80% for 45 newborns with NTDs whose mothers did not use FA.

Conclusion: Our results revealed that the mean birth weight was lower while the incidence of meningomyelocele was significantly higher in newborn infants whose mothers did not use FA.

Keywords: Folic Acid; Pregnancy; Meningomyolocele; Spina Bifida.

INTRODUCTION

Neural tube defects (NTD) are birth defects that originate during embryonic development, affecting the spinal cord and brain. In the early stages of pregnancy, there is a line behind the embryo, which is composed of nerve tissue. As the fetus grows, the spinal cord, nerve system, and brain are formed along this line. In the meantime, bone tissue begins to encircle the spinal cord. If any defect develops during the developmental period, several anomalies can occur. The worst case is the absence of major parts of the brain, which is known as anencephaly (1).

NTDs are among the most common congenital anomalies of the central nervous system (CNS) and develop in the first month of pregnancy due to late or no closure of the neural structures. NTDs may develop concomitantly with anomalies such as meningomyelocele, spina bifida occulta, spina bifida aperta, meningocele, encephalocele, anencephaly, dermal sinus, tethered cord, syringomyelia, and diastematomyelia. Although predisposing factors for NTDs are not certainly known, factors such as hyperthermia, use of drugs (e.g., valproic acid) in pregnancy, folic acid (FA) deficiency, genetic anomalies in the FA pathway, various chemicals, malnutrition, maternal obesity, or diabetes are associated with the development of NTDs (2). Intake of FA supplement in the early stages of pregnancy significantly decreases the incidence of NDT (3). Most studies in the literature examined the effects of FA use on the development of NTDs (3,4).

The objective of this study was to investigate the rate of NTD and the clinical features of newborns of mothers who did not use FA in their pregnancies.

MATERIAL and METHODS

After ethical approval was obtained from the ethics committee of clinical research our hospital, the data of a total of 82 newborns aged 1to 16 days , who were

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diagnosed with meningomyelocele and operated between January 1, 2012, and January 1, 2017, were retrospectively examined. Newborns were divided into two groups depending on whether their mothers used FA (Group 1) during pregnancy or not (Group 2). Demographic data on newborns such as age, sex, and clinical data such as time of diagnosis, delivery method, maternal FA use, comorbidity in the mother, type and location of meningocele, comorbidity in the newborn, developed scoliosis, hydrocephalus, cerebrospinal fluid fistulas, and tethered cord syndrome, routine hemogram; Red Blood Cell (RBC, Hemoglobin (Hbg), Hematocrit(Htc), White Blood Cell (Wbc), Platelet (PLT), Natrium (Na), Potassium (K), and Biochemical Values C-Reactive Protein (CRP), Glucose, Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), Gamma Glutamyl Transferase (GGT) AND Creatinine were recorded. The number of malformations such NTD and biochemical values were compared.

Statistical analysis was performed using SPSS 21.00 for Windows. Compliance of numeric data with normal distribution was analyzed using Kolmogorov–Smirnov test. The comparison of data with normal distribution was performed using Student's t-test. Chi-square test was used in the comparison of categorical data. Also multivariate lineer analysis wasperformed for the effect of FA usage on C/S section ratio. For the comparison of all data, $P < 0.05$ was considered statistically significant.

RESULTS

Of a total of 82 newborns, 43 (52.4%) females and 39 (47.6%) males were included in the study. The mothers of 37 (45.1%) newborns used FA during the antenatal period, whereas those of 45 (54.9%) newborns did not.

The mean birth weight of the newborns whose mothers used FA was 2.33 ± 0.29 kg, whereas that in newborns whose mothers did not use FA was 2.13 ± 0.28 kg. The difference was statistically significant ($P = 0.004$). Patients' age, birth height, and laboratory data are shown in Table 1.

Table 1. Clinical and laboratory characteristics of the newborns

	Folic acid use during pregnancy	N (%)	Mean ± Std. Deviation		p
Age (day)	no	45 (54.9%)	7.76	± 3.113	0.620
	yes	37 (45.1%)	7.44	± 2.512	
Weight (kg)	no	45 (54.9%)	2.13	± 0.28	0.004
	yes	37 (45.1%)	2.33	± 0.29	
Height (cm)	no	45 (54.9%)	50.62	± 1.85	0.061
	yes	37 (45.1%)	51.31	± 1.39	
AST U/L	no	45 (54.9%)	60.96	± 33.859	0.766
	yes	37 (45.1%)	63.47	± 40.537	
ALT U/L	no	45 (54.9%)	28.29	± 17.536	0.700
	yes	37 (45.1%)	30.03	± 21.898	
Ca mg/dL	no	45 (54.9%)	8.66942	± .832748	0.747
	yes	37 (45.1%)	8.73250	± .899465	
Cre mg/dL	no	45 (54.9%)	0.5022	± 0.17706	0.300
	yes	37 (45.1%)	1.3928	± 5.07763	
CRP mg/L	no	45 (54.9%)	3.5442	± 4.37299	0.772
	yes	37 (45.1%)	3.2625	± 4.30451	
GGT U/L	no	45 (54.9%)	101.84	± 78.389	0.512
	yes	37 (45.1%)	115.19	± 99.221	
Glucose mg/dL	no	45 (54.9%)	91.417	± 28.7138	0.069
	yes	37 (45.1%)	79.978	± 24.5370	
HBG g/dL	no	45 (54.9%)	15.20	± 4.43	0.874
	yes	37 (45.1%)	15.35	± 4.23	
HTC %	no	45 (54.9%)	43.44	± 15.98	0.958
	yes	37 (45.1%)	43.62	± 15.66	
K mmol/L	no	45 (54.9%)	4.9927	± 1.40083	0.626
	yes	37 (45.1%)	4.8347	± 1.47688	
MPV fl	no	45 (54.9%)	9.244	± 1.0621	0.371
	yes	37 (45.1%)	9.056	± .8279	
Na mmol/L	no	45 (54.9%)	138.69	± 6.708	0.159
	yes	37 (45.1%)	140.75	± 6.281	
NEU 10^9/L	no	45 (54.9%)	10.49	± 10.92	0.069
	yes	37 (45.1%)	7.36	± 2.67	
PLT 10^9/L	no	45 (54.9%)	311.13	± 106.86	0.375
	yes	37 (45.1%)	334.64	± 125.71	
RBC,10^{12}/L	no	45 (54.9%)	4.70	± 1.07	0.335
	yes	37 (45.1%)	4.89	± 0.78	
WBC 10^9/L	no	45 (54.9%)	14.91	± 3.43	0.725
	yes	37 (45.1%)	15.16	± 3.03	

AST: Aspartate Amino Transferase, ALT: Alanine Amino Transferase, Ca: Calcium, Cre: Creatinine, CRP. C-ReactiveProtein, GGT: Gamma Glutamyl Transferase, HBG: Hemoglobin, HTC: Hematocrit, K: Potassium, MPV: Mean Platelet Volume, Na: Natrium, NEU: Neutrophil, PLT: Platelets, RBC: Red Blood Cell, WBC: White Blood Cell

Of 45 newborns whose mothers did not use FA during pregnancy, 23 (51.1%) were delivered via cesarean section, and of 37 newborns whose mothers used FA during the pregnancy, 9 (24.3%) were delivered via cesarean section; the difference was statistically significant (P = 0.017).

For 45 newborns with NTDs whose mothers did not use FA, the incidence of meningomyelocele was 80% (N = 36) and that of meningocele was 20% (N = 9); the difference was significant (P = 0.001). Of the 22 (48.8%) had paraparesis, 13 (28.9%) had monoparesis, and 10 (22.2%) had paraplegia in newborns whose mothers did not use FA during pregnancy. Paraparesis was significantly dominant in terms of neurological deficiency (P = 0.006).

Of 45 newborns whose mothers did not use FA during pregnancy, 16 (%) had dermal sinus, and of 36 newborns whose mothers used FA, 22 (%) had dermal sinus (P = 0.022). A total of 22 cesarean deliveries were performed in both groups.In 18 patients, indication for cesarean was due to fetal anomaly (NTD), in 3 placenta previa and in 1 transverse presentation. As the number of women using FA increases, the number of S/C sectio decreases. In other words, there was a significant negative relationship between FA use and S / C section (P <0.001). Multivariate linear analysis for the effect of FA usage on C/S section ratio was revealed as 0.516. Other clinical and demographic characteristics of the newborns are shown in Table 2.

Table 2. Demographic and Clinical characteristics of the newborns

		Folic acid use during pregnancy				
		no		yes		P
		n	(%)	n	(%)	
Sex	Female	27	(60.0)	16	(44.4)	0.163
	Male	18	(40.0)	20	(55.6)	
Time of Diagnosis	<1 week	31	(68.9)	18	(50.0)	0.184
	1 weekto 1 month	14	(31.1)	18	(50.0)	
Delivery method	vaginal	22	(48.9)	27	(75.0)	0.017
	c-section	23	(51.1)	9	(25.0)	
Maturity	premature	26	(57.8)	19	(52.8)	0.653
	term	19	(42.2)	17	(47.2)	
Localization	sacral	25	(55.6)	13	(36.1)	0.196
	lumbar	16	(35.6)	17	(47.2)	
	thoracic	4	(8.9)	6	(16.7)	
Type	meningocele	9	(20.0)	20	(55.6)	0.001
	meningomyelocele	36	(80.0)	16	(44.4)	
Neurologicaldeficit	monoparesis	13	(28.9)	23	(63.9)	0.006
	paraparesis	22	(48.9)	10	(27.8)	
	paraplegia	10	(22.2)	3	(8.3)	
Scoliosis	no	26	(57.8)	27	(75.0)	0.105
	yes	19	(42.2)	9	(25.0)	
Hydrocephalia	no	24	(54.5)	12	(33.3)	0.058
	yes	20	(45.5)	24	(66.7)	
Ventriculomegaly	no	17	(37.)8	14	(38.9)	0.919
	yes	28	(62.2)	22	(61.1)	
Operation date	<1 week	3	(6.7)	8	(22.2)	0.094
	1 week to 1 month	25	(55.6)	14	(38.9)	
	1 month to 2 months	17	(37.8)	14	(38.99)	
Treatmentmethod	surgical	45	(100)	36	(100.09	
Additional pathology	no	2	(4.4)	0	(0.09)	0.200
	yes	43	(95.6)	36	(100.)	
Tethered cord syndrome	no	29	(64.4)	21	(58.3)	0.574
	yes	16	(35.6)	15	(41.7)	
Dermal sinus	no	29	(64.4)	14	(38.9)	0.022
	yes	16	(35.6)	22	(61.1)	
Maternal illness	no	44	(97.8)	36	(100.)	0.368
	yes	1	(2.2)	0	(0.0)	
BOS fistula	no	41	(91.1)	36	(100)	0.067
	yes	4	(8.9)	0	(0.0)	

±Chi-square

DISCUSSION

In our study, we found that the mean weight rate of newborns whose mothers did not use FA was lower and cesarean section rate was higher. In newborns with NTDs whose mothers did not use FA, the most common anatomic localization was meningomyelocele. The most common neurologic deficit in the newborns with NTDs was paraparesis. Additionally, multivariate linear analysis for the effect of FA usage on C/S section ratio was revealed as 0.516.

The incidence of NTD was associated with race, ethnic origin, geographical region, and socioeconomic condition. The incidence is 11.7:10.000 in Africa, 9:10.000 in Europe, and 3.3:10.000 in America (5). Folate has a significant role as a co-enzyme in numerous biochemical pathway involved in metabolism of methylation, including the synthesis of DNA, RNA, and certain amino acids. Unique amounts of folate are required during pregnancy because of the rapid rate of cellular and tissue growth and development for the mother, placenta, and fetus (6). FA use during pregnancy can prevent NTD development. A study by Caudill et al. showed that FA-enriched diet helps fertile women achieve positive folate balance, and their red cell folate concentrations reach a certain level that decreases the frequency of NTD (7).

Considering the contributions of folate in DNA synthesis and gene expression, it can also play important roles in the development of the fetal CNS. In general, it can be stated that not all NTDs can be prevented by folic acid, and studies conducted until now could not explain the metabolic mechanisms that underlie human FA reactions in NTDs (8). Randomized controlled trials and large scale cohort studies have shown the preventive effects of folic acid use by mothers against NTDs in newborns (9). Contrary to this, in a prospective cohort study in Japan, no significant correlation was found between the nationwide FA supplement use and the incidence of NTDs in Japan (10). That being said, studies show that folic acid supplement use in pregnancy decreases delayed speech and autism risk in newborns (11). It is also reported that folic acid use during pregnancy results in decreased incidence of NTDs in developing countries (12). In a study in Turkey, in the examination of NTDs based on regions, the highest incidences were found in North and East Anatolia and the lowest in Western Anatolia (13).

In our study, contrary to the literature, vaginal delivery rate was 48.9% (1,15). Meningomyelocele localization was most frequent in the lumbosacral region, which is compatible with the literature. Based on the distribution of sex, we found that meningocele and meningomyelocele were more common in females, which is compatible with the literature (1,15).

It was observed that 50% of our patients were operated within the first month, which is compatible with the literature. Non-use of FA during pregnancy increases the risk of meningomyelocele and concomitant congenital NTDs in newborns and results in decreased birth weight. The incidence of NTDs is high in Turkey due to malnutrition and drug intake. The most common complication is meningomyelocele (13).

In pregnant women who do not use FA, anomalies such as ventriculomegaly, dermal sinus, scoliosis, and tethered cord syndrome seem to be higher. In newborns with meningomyelocele, the incidence of concomitant malformations such as tethered cord syndrome and dermal sinus as well as hydrocephalus is high, and these malformations result in increased morbidity rates (15). In newborns with meningomyelocele, early surgical treatment of malformations such as hydrocephalus, tethered cord syndrome, and dermal sinus can prevent the development of orthopedic problems in the future.

There are some limitations to our study-the limited number of study and control patients included in the study, absence of folic acid dosage and duration of FA treatment in pregnancy in our records, and the retrospective nature of our study.

CONCLUSION

Our results reveal that the mean birth weight were lower while the incidence of meningomyelocele was significantly higher in newborn infants whose mothers did not use FA. In countries such as Turkey, preventive medicine must be generalized and preventive medicine specialists and pregnant women must be educated on the importance of folic acid supplement intake.

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